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SHORT COMMUNICATIONS

Characteristics of the Blood Oxygen Transport Function in Angina Pectoris Patients Receiving Treatment Aimed at Correcting the L-Arginine–NO Pathway

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Abstract—The oxygen transport function of the blood was studied in angina pectoris patients treated with nitrosorbide to correct the L-arginine–NO pathway. A series of parameters (the O_2 content of venous blood, blood oxygen capacity, blood oxygenation level, methemoglobin content, oxygen affinity of methemoglobin, and central hemodynamic parameters) were determined. The oxygen affinity of hemoglobin in patients with functional class I and II stable exertional angina decreased according to the severity of the disease and, therefore, can be considered a criterion of an unfavorable course of the disease. Nitrosorbide therapy resulted in an increase in the oxygen affinity of hemoglobin.

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INTRODUCTION

In recent years, changes in the endothelial function, particularly, changes in the L-arginine–NO pathway, ensuring optimum NO generation, have been considered to be of great importance in the pathogenesis of coronary heart disease (CHD), arterial hypertension, and other diseases. Disorders of the oxygen transport function of the blood (OTFB) are also of great importance in the development of these pathologies [1]. The problem of investigation of the physiological effects of NO acquired a new aspect, namely, the interaction of NO with different blood components, including hemoglobin. There are three main NO-containing hemoglobin derivatives: nitrosylhemoglobin, nitrosohemoglobin, and methemoglobin. These compounds differently influence the oxygen affinity of hemoglobin (OAH), which is of great importance for gas exchange processes [2]. However, the state of the OTFB, especially, in dependence on the severity of CHD, remains largely unknown, and the results of several relevant studies are contradictory [3]. Nitric drugs used in cardiology act not only through NO-dependent mechanisms and the regulation of the vascular tone and blood flow volume, but also through interaction with hemoglobin [2].

The objective of this work was to study the state of the OTFB in patients with stable exertional angina (SEA) whose L-arginine–NO pathway, in the given case, was corrected by nitrosorbide therapy.

MATERIALS AND METHODS

We studied 45 SEA inpatients (functional classes (FCs) I–III). The mean age of the patients was 52.9 ± 1.13 years. To ensure group uniformity, we examined only male patients. Patients with any associated pathology directly influencing the OTFB were excluded from the analysis. The effect of two-week nitrosorbide therapy (40 mg per day) was assessed for 15 SEA patients (FC II). The control group comprised 28 male donors aged from 35 to 55 years.

Upon the admission to the hospital and at the end of the treatment, we took blood from the ulnar vein of the patients immediately after the recovery of the outflow. For each blood sample, we determined oxygen tension (pO_2), CO_2 tension (pCO_2), and pH using an ABL-330 gas analyzer (Radiometer). The buffer base excess (BE) and standard bicarbonate (SBC) were calculated using Siggaard-Andersen charts. Using a polarimeter, we also estimated the O_2 content in the blood (C_vO_2) and oxygen capacity (OC); the values obtained were used to estimate the blood oxygenation level (SO_2). The OAH was estimated by the $p50$ parameter (pO_2 value at a blood oxygenation of 50%) determined using the method of mixing [4] at 37°C, pH 7.4, and a pCO of 40 mm Hg ($p50_{stand}$). The $p50$value for the actual pH, pCO_2, and temperature ($p50_{real}$) was calculated on the basis of the $p50_{stand}$ value according to [4] at a temperature coefficient of 0.24. The methemoglobin content (MetHb) was determined spectrophotometrically; 2,3-diphosphoglycerate (2,3-DPG) was investigated using nonenzymatic tehcniques.

The parameters of central hemodynamics were determined by the tetrapolar rheography method and were used to calculate the stroke index (SI) and stroke volume index (SVI). The system oxygen capacity (SOC) was calculated using the following formula:

Indices of the oxygen transport function of the blood and the oxygen transport system in patients with SEA of FCs I–III ($M \pm m$)

Indices	Control group	FC I SEA	FC II SEA	FC III SEA
n	28	13	15	17
MetHb, %	0.593 ± 0.069	0.42 ± 0.039	0.67 ± 0.075	0.61 ± 0.079
pO_2, mm Hg	36.01 ± 1.39	35.9 ± 1.49	28.8 ± 1,24Ψ,*	27.5 ± 1,11Ψ,*
C_vO_2, vol %	12.30 ± 0.54	12.47 ± 1.80	9.35 ± 0,74Ψ,*	9.86 ± 0,76Ψ,*
OC, vol %	20.59 ± 0.34	20.60 ± 0.80	22.35 ± 0.68	20.99 ± 0.75
SO_2, %	62.39 ± 2.45	53.04 ± 3,61Ψ	45.46 ± 2,76Ψ	46.79 ± 2,86Ψ
$p50_{real}$, mm Hg	28.42 ± 0.31	34.9 ± 109Ψ	31.2 ± 0,90Ψ,*	28.2 ± 0.71*,#
$p50_{stand}$, mm Hg	26.64 ± 0.32	34.0 ± 0,97Ψ	29.2 ± 0,67Ψ,*	26.9 ± 0.85*, #
2,3-DPG, μM/ml	4.19 ± 0.096	6.80 ± 0,403Ψ	5.76 ± 0,508Ψ	4.54 ± 0.34*
pCO_2, mm Hg	47.46 ± 1.05	40.2 ± 1,96Ψ	45.03 ± 1.82	47.4 ± 1.92
pH	7.326 ± 0.005	7.372 ± 0,011Ψ	7.354 ± 0.015	7.357 ± 0.012
SBC, mM	41.23 ± 1.12	46.66 ± 1.31	48.40 ± 1.09	48.55 ± 0.63
BE, mM	0.92 ± 0.12	1.35 ± 0.38	0.33 ± 0.92	0.52 ± 0.69
SI, mm/m^2	37.12 ± 2.80	36.21 ± 3.30	34.26 ± 2.0	28.38 ± 2.39
SVI, l/(min m^2)	2.89 ± 0.17	2.51 ± 0.10	2.15 ± 0.10	1.91 ± 0.15*
VO_2, cm^3/min	352.4 ± 29.88	354.5 ± 72.60	373.4 ± 33.16	399.2 ± 31.12
OUC, ml/min	0.403 ± 0.0312	0.468 ± 0.0362	0.544 ± 0.0367	0.531 ± 0.0280
SOC, ml/min	875.1 ± 51.14	719.2 ± 92.21	732.8 ± 62.14	748.3 ± 39.81
VOR, ml/min	522.7 ± 34.20	364.3 ± 29.94	35.91 ± 48.30	349.1 ± 27.0

Note: For abbreviations, see the text; Ψ, in comparison with the control value; *, in comparison with FC I SEA; #, in comparison with FC II SEA.

$SOC = \frac{CO}{100} C_aO_2$, , where CO is the cardiac output (ml) and C_aO_2 is the O_2 content in 100 ml of arterial blood. To estimate the efficiency and functioning of the OAH, the oxygen utilization coefficient (OUC) and the volume of venous oxygen return (VOR) were determined: $OUC = \frac{SOC - VOR}{SOC}$, $VOR = S_vO_2 \times \frac{CO}{100}$. [5].

The statistical treatment of the data obtained was carried out using a PC and the StatGraphics statistical software.

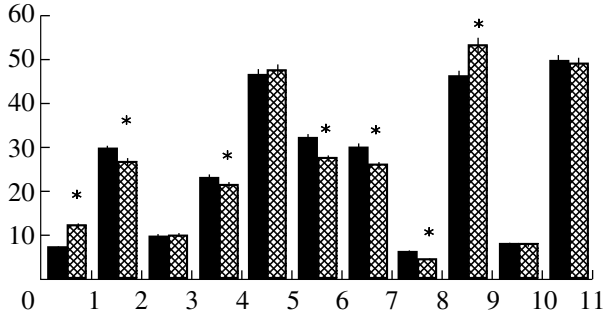
RESULTS AND DISCUSSION

The table shows that, compared to healthy subjects, patients with FC I SEA exhibited a decrease in S_vO_2 and pCO_2 and an increase in the pH of the blood and $p50$ value (by 27.6%). Probably, this is a typical tissue reaction to hypoxia caused by coronary circulatory insufficiency. This is confirmed by an increase in the 2,3-DPG content in red cells ($p < 0.01$), which, in most cases (11 patients), was correlated with the $p50$ value. The values of other parameters did not differ from those of healthy subjects.

In the case of patients with FC II SEA, the OAH value was also decreased ($p50_{stand}$ increased by 9.7% compared to the control group), but was lower by 14.1% ($p < 0.001$) than that of the previous group. Probably, this was caused by a certain "exhaustion" of the compensatory reaction of the body, which is confirmed by both a smaller (in comparison with the previous group) increase in the 2,3-DPG content in red cells ($p < 0.05$) and a decrease in the pO_2, C_vO_2, and S_vO_2 values. The above-mentioned OTFB indices did not depend significantly on the state of central hemodynamics since these indices were the same in both groups of SEA patients (FCs I and II). At the same time, the MetHb content in both groups of SEA patients also did not differ significantly from that of the control group.

As the severity of the disease increased (FC III), the $p5$ value did not differ from that of healthy subjects. Probably, this fact can be considered a criterion of an unfavorable course of the disease because conditions for worsening of oxygenation are formed. At the same time, the pO_2, C_vO_2, and S_vO_2 values were lower than in the control group.

A decrease in OAH in patients with FC II SEA should be considered as a compensatory reaction of tissues to hypoxia caused by coronary circulatory insufficiency. The rightward shift of the oxyhemoglobin dissociation curve (OAH decrease) provided better blood deoxygenation and, obviously, optimized the tissue oxygen consumption rate [10]. On the contrary, during severe hypoxia (FC III), this curve shifted leftwards, ensuring, to some degree, the maintenance of prooxi-



Indices of the OTFB in patients with FC II SEA during nitrosorbide therapy ($M \pm m$, $n = 15$). Black and white bars show the indices before and after the treatment, respectively. The abscissa shows (*1*) MetHb, %; (*2*) pO_2, mm Hg; (*3*) C_vO_2, vol %; (*4*) OC, %; (*5*) SO_2, %; (*6*) $p50_{real}$, mm Hg; (*7*) $p50_{stand}$, mm Hg; (*8*) 2,3-DPG, μM; (9) pCO_2 mm Hg; (*10*) pH; (*11*) SBC, mM. * Significant differences between the values before and after nitrosorbide therapy.

dant–antioxidant equilibrium and, possibly, exerting a marked antioxidant effect in the case of significant disorders in oxygen utilization in tissues.

After nitrosorbide therapy, we observed a decrease in the $p50_{stand}$ value with a corresponding leftward shift of the oxyhemoglobin dissociation curve. At the same time, we recorded a reduction of pO_2 and pH; pCO_2 and MetHb content values increased from 0.67 ± 0.075 to $1.182 \pm 0.186\%$, $p < 0.01$ (figure). This nitrosorbide influence on the OAH was especially pronounced in patients with a high pretreatment $p50_{real}$ value ($31.2 \pm$ 0.9 mm Hg or more). This blood parameter changed simultaneously with a decrease in the 2,3-DPG concentration. It is known that nitrosorbide is an endogenous source of NO, and its generation plays an important role in vascular tone regulation and blood flow increase. Probably, this is why nitrosorbide therapy optimizes the OTFB state. In the case of endothelial dysfunction, it is possible to maintain normal vascular function via NO inhalation, which results in the formation of different NO derivatives of hemoglobin and subsequent NO release in different parts of the body [6]. We also consider that NO can influence the oxygen-binding properties of hemoglobin not only through indirect hemodynamic mechanisms, but also through a direct interaction with hemoglobin, resulting in the formation of different NO derivatives and, therefore, in a change in the OAH [7]. This is confirmed by the pattern of changes in the methemoglobin level. During the assessment of the NO–hemoglobin interaction, the former is considered to be an OAH-determining ligand. The revealed positive effect of the therapy performed, based on the modification of the L-arginine–NO pathway, namely, nitrosorbide therapy, is obviously mediated by changes in the OAH via an NO-dependent mechanism. The influence of NO on the formation of oxygen-binding blood properties via the formation of different NO–hemoglobin compounds, vascular tone regulation, and the action of peroxynitrite may be very important for maintenance of gas exchange processes and other physiological functions.

SPELL: OK

CONCLUSIONS

According to our data, changes in the OAH in SEA patients depend on the severity of the disease. At early stages of the disease (FCs I and II), we observed a decrease in this parameter. As the disease grew progressively worse (FC III), we recorded more pronounced disorders in the regulation of the oxygen-binding properties of hemoglobin.

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